Remarks

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1, 4, 9-11, 19, and 23 are amended, claims 55-58 are added, and claims 5-7, 12-18, 22, 38-40, and 44-45 are canceled. Claims 1-4, 8-11, 19-21, 23-37, 41-43, and 46-58 are now pending in this application. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the above-identified application.

Claims 12-18, 22, 38-40, and 44-45 are canceled solely in response to the Restriction Requirement and without prejudice to their prosecution in a divisional application of the above-identified application.

Amended claims 1, 4, 9-11, and 19 are supported by originally-filed claims 1, 4 , 9-11, and 19, respectively, and at page 10, lines 9-12 and 19-24, page 12, lines 3-6, and Figure 20 of the specification.

Amended claim 23 is supported by originally-filed claim 23.

New claims 55-56 are supported at page 10, lines 9-12 and 19-24, page 12, lines 3-6 and Figure 20 of the specification.

New claims 57-58 are supported at page 91, lines 9-18 and Figure 20 in the specification.

Substitute drawings, which address the objections to the drawings specified on Form PTO 948, are enclosed herewith.

The Examiner rejected claims 1, 4-7, 9-11, and 46-47 under 35 U.S.C. § 102(e) as being anticipated by Engelhardt et al. (U.S. Patent No. 6,436,392). The Examiner also rejected claims 1, 4-7, 9-11, and 46-47 under 35 U.S.C. § 102(e) as being anticipated by Couto et al. (U.S. Patent No. 6,200,560) or Couto et al. (U.S. Patent No. 6,221,349). The Examiner further rejected claims 1, 4-5, 9-11, 19-20, 22, and 46-47 under 35 U.S.C. § 102(b) as being anticipated by Rendahl et al. (Nature Biotechnology, 16:757 (1998)). These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

It is disclosed in the '392 patent that recombinant adeno-associated virus (rAAV) vectors, each containing a promoter and an open reading frame, may become linked after infection of the host cell with the vectors and synthesis of double-stranded viral DNA (column 4, lines 41-56 and

column 5, lines 26-38). Other vectors disclosed in the '392 patent include rAAV vectors that contain an open reading frame flanked by a splice site, i.e., one rAAV vector contains a splice acceptor site and another rAAV vector contains a splice donor site, which vectors together encode a functional gene product (column 4, lines 57-column 5, line 25). It is disclosed that transcription of a molecule formed by linking the two rAAVs in a cell results in a spliced RNA molecule which encodes a functional peptide (column 49, lines 14-22).

The '560 patent issued from an application which is a continuation-in-part of the application which issued as the '349 patent. The '560 and '349 patents teach the use of rAAV vectors encoding Factor VIII or a fragment thereof, i.e., a fragment encoding only one chain of Factor VIII which may not be biologically active until administered to a subject that can supply the missing chain (column 20, lines 1-19 of the '349 patent and column 20, lines 13-31 of the '560 patent). Example 1 of the '560 and '349 patents discloses two AAV vectors, each of which delivers different portions of the Factor VIII gene to cells. Both vectors employ the EF1α promoter and intron to express a fragment of Factor VIII, i.e., the heavy chain of Factor VIII or the light chain of Factor VIII (Figure 7).

The Rendahl et al. article discloses two rAAV vectors, one having a tetracycline sensitive operator sequence linked to a minimal CMV promoter which controls expression of a murine erythropoietin transgene, and the other having a CMV promoter controlling expression of a tetracycline responsive transactivator (abstract and Figure 1). The two rAAVs were coinjected directly into the skeletal muscle of adult immunocompetent mice (abstract). It is disclosed that transcription of the murine erythropoietin transgene was controlled by systemic administration or withdrawal of tetracycline over an 18 week period, demonstrating that the two vectors were capable of transducing the same cell (abstract).

None of the cited art, i.e., the'392 patent, the '560 patent, the '349 patent or Rendahl et al., teach a composition comprising at least two rAAVs, wherein one of the rAAVs comprises an open reading frame and the other rAAV comprises at least one *cis*-acting heterologous transcriptional regulatory element, wherein the *cis*-acting heterologous transcriptional regulatory element regulates expression of the open reading frame after a host cell is contacted with the at least two vectors. Moreover, Rendahl et al. do not disclose a rAAV vector comprising at least

one *cis*-acting heterologous transcriptional regulatory element functional in a host cell, which vector regulates, in the host cell, expression of a therapeutic gene in a second rAAV.

Accordingly, withdrawal of the § 102 rejections is respectfully requested.

The Examiner also rejected claims 1, 4-7, 9-11, and 46-47 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of Engelhardt et al. (U.S. Patent No. 6,436,392). This rejection is respectfully traversed.

Claim 8 of the '392 patent is directed to a method to express a polypeptide in a host cell. The method comprises contacting a host cell comprising a first AAV vector comprising linked: i) a first DNA segment comprising a 5'-inverted terminal repeat (ITR) of AAV; ii) a second DNA segment comprising a splice acceptor site; iii) a third DNA segment comprising a portion of an open reading frame for a polypeptide; and iv) a fourth DNA segment comprising a 3'-ITR of AAV; with a second AAV vector comprising linked: i) a first DNA segment comprising a 5'-ITR of AAV; ii) a second DNA segment comprising a splice donor site; iii) a third DNA segment comprising a portion of an open reading frame which together with the DNA segment of (a)(iii) encodes a functional polypeptide; and iv) a fourth DNA segment comprising a 3'-ITR of AAV so as to yield a host cell which expresses the functional polypeptide.

Claim 9 of the '392 patent is directed to a method to express a polypeptide in a host cell, comprising: contacting a host cell with a first AAV vector comprising linked: a) i) a first DNA segment comprising a 5'-ITR of AAV; ii) a second DNA segment comprising a portion of an open reading frame operably linked to a promoter; iii) a third DNA segment comprising a splice donor site; and iv) a fourth DNA segment comprising a 3'-ITR of AAV; and a second AAV vector comprising linked: b) i) a first DNA segment comprising a 5'-ITR of AAV; ii) a second DNA segment comprising a splice acceptor site; iii) a third DNA segment comprising a portion of an open reading frame which together with the DNA segment of a) ii) encodes a functional polypeptide; and iv) a fourth DNA segment comprising a 3'-ITR of AAV; so as to yield a host cell which expresses the functional polypeptide. Claims 10-15 are dependent, in part, on claims 8-9.

Claims 8-15 of the '392 patent do not disclose or suggest a composition comprising at least two rAAVs, wherein one of the rAAVs comprises an open reading frame and the other rAAV comprises at least one *cis*-acting heterologous transcriptional regulatory element, wherein

the *cis*-acting heterologous transcriptional regulatory element regulates expression of the open reading frame after the host cell is contacted with the at least two vectors.

Hence, withdrawal of the obviousness-type double patenting rejection is appropriate and respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6959) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

JOHN F. ENGELHARDT ET AL.,

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
612-373-6959

Date August 11, 2003

By

Janet E. Embretson
Reg. No. 39,665

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 11 day of August, 2003.

Candis B. Buending

Name

Signature